REMARKS

By amendment above, previously withdrawn claims 38-47 have been cancelled. Claims 29, 31 and 32 have been amended. Support for the amendments to claim 29 can be found in the first full paragraph of the Detailed Description of the Invention on page 7 of the specification and in claims 31 and 32 as previously presented. In view of the amendments to claim 29, claims 31 and 32 have been amended. New claims 48 and 49 have been added. Support for these claims can be found in claims 37 and 31, respectively. No new matter has been introduced into the application through any of the foregoing amendments.

Claims 29 and 34-37 have been rejected under 35 U.S.C. § 102(b) as anticipated by Bersani. The examiner asserted that the reference teaches the administration of melatonin and zolpidem to patients, all of whom showed a significantly longer sleep duration when compared to their normal sleep patterns and that this teaches the potentiation of a hypnotic effect in a patient in need thereof. This rejection is traversed.

By amendment above, claim 29 has been amended to make explicit that the administration of melatonin in combination with a non-benzodiazepine hypnotic such as zolpidem serves to promote sleep initiation in patients who have difficulty falling asleep. This reduction in sleep latency achieved by the present invention is not taught or suggested by the Bersani reference. As the examiner noted, Bersani teaches that patients in his study showed an increase in sleep duration after 30 days of treatment with 3 mg. of melatonin in combination with their normal regimen in

comparison to treatment with their normal regimen in the absence of melatonin. There is no indication that any of the patients in the Bersani study experienced a reduction in sleep latency; indeed, even if a patient did experience a change in sleep latency there would be no way to know what drug or combination of drugs was the cause of that change. The Bersani reference thus does not anticipate claim 29 or any of claims 34-37.

Claims 29 and 34-37 also have been rejected under 35 U.S.C. §102(b) as anticipated by Suhner. The examiner characterized Suhner as teaching the co-administration of 5 mg melatonin and 10 mg zolpidem to transcontinental airline passengers crossing 6-9 time zones, i.e., a patient population known to suffer from jet-lag. The examiner further characterized the reference as providing a number of data points over the 5 treatment days which showed a potentiated hypnotic effect in those patients who received both melatonin and zolpidem as compared to those who received only zolpidem. The examiner focused on the data points presented for sleep latency on night 3 at home, the number of awakenings on night 2 and wakeful periods after sleep onset on days 1, 2 and 4, each of which were said to be commonly used as measures of a hypnotic effect. This rejection is traversed.

The Suhner reference focuses on efforts to reduce jet-lag. Subjects in the study were administered zolpidem, melatonin or a combination thereof on a transatlantic flight and then once daily at bedtime for 4 consecutive days post-flight. The subjects self-rated a number of factors, including overall sleep quality, number of awakenings, duration of waking after sleep onset, wake-up time and sleep latency.

The authors report that zolpidem treatment alone was rated the *most effective jet lag medication*. Although the examiner

asserted that "a number of data points over the 5 treatment days showed a potentiated hypnotic effect in a patient ... in the melatonin + zolpidem cohort vs. the zolpidem cohort," basing conclusions on particular data points is not a scientific approach, and although the examiner flagged five data points as showing a potentiated hypnotic effect resulting from zolpidem and meltaonin administration, there are fifteen data points in which the co-treatment of zolpidem and melatonin resulted in a smaller effect compared to those of zolpidem and melatonin alone. Thus, a review of the data in total does not support the examiner's conclusion. The examiner has picked and chosen selected data points to support her hypothesis, but that is not a proper or scientifically appropriate approach to drawing conclusions about the data presented.

In addition, the claims as amended above now focus on improving sleep initiation. Suhner does not teach or suggest that the combination of melatonin and another drug, such as zolpidem, are useful in decreasing sleep latency. The table with the data points on which the examiner relives shows that the combination of zolpidem and melatonin improved sleep latency only on night 3; the other nights either zolpidem alone was better or there was no difference between zolpidem alone and melatonin. The present claims now also require the administration of melatonin in sustained release form; neither Suhner nor Bersani teach or suggest such a mode of administration or form for melatonin delivery.

Claims 30-31 have been rejected under 35 U.S.C. §103 as unpatentable over the Suhner reference discussed above in view of Ohkawa, U.S. Patent 6,348,485. The Suhner reference was relied upon as in the preceding rejection; Ohkawa was cited as teaching

the administration of a melatonin agonist and zolpidem in a single pharmaceutical formulation form or as separate dosage forms. The examiner asserted that the motivation to combine the teachings of the two references lies in the teaching by Ohkawa of methods for increasing the effects of, and allowing for the reduction in the dose of certain drugs, such as zolpidem. The examiner asserted that, as such, it would have been obvious to use the drug combination taught by Suhner, melatonin and zolpidem, in a single formulation as taught by Ohkawa to create the invention of claims 30 and 31. This rejection is traversed.

The weaknesses of the Suhner reference have been discussed above, and that discussion is equally applicable to the present rejection. Ohkawa does not compensate for the deficiencies of the primary reference. Ohkawa provides that the administration of a particular melatonin agonist, (S)-N-[2-(1,6,7,8-tetrahydro-@H-indeno[5,4-b]furna-8-yl)ethyl]proponamide (frequently called Compound A in the reference), in combination with either a selected non-benzodiazepine drug (zolpidem or zopiclone) or benzodiazepine drug (triazolam or brotizolam) to treat a lengthy list of a variety of illnesses or conditions, including sleep disorders, such as primary insomnia. The only more detailed description regarding the administration of these compounds to affect sleep appears in the Experimental Example, which bridges columns 9 and 10, where Ohkawa and his co-inventor teach that the administration of the selected melatonin agonist, Compound A, and triazolam to crab-eating macaques. The patentees state that they classified the sleep-wake stages as progressing from stage W (i.e., wakefulness), stage 1+2, stage 3, stage 4 and, finally, stage rapid eye movement (REM). The patentees state that the administration of either compound alone did not have any

significant effect on any of the sleep latencies, but that the combined administration shortened the latencies of deep slow wave sleep, i.e., stage 3 and stage 4, and significantly shortened the latency of the stage 4 sleep. This is of no relevance to the present claims, which are directed to improving sleep initiation. One of skill in the art reading this reference would come away only believing that stage 3 and stage 4 sleep can be affected by the administration of the particular melatonin agonist and one of the other specified compounds. The combination of this teaching with the disclosures of the primary reference does not suggest the presently claimed method.

Claims 32 and 33 have been rejected under 35 U.S.C. §103(a) as unpatentable over Suhner in view of Ohkawa, as applied to claims 30 and 31 above, taken further in view of Richardson, U.S. Patent 6,042,849. As noted, the examiner relied upon the primary and secondary references as she had in the preceding rejection. The tertiary reference was cited as teaching a dual layer tablet which has an immediate release layer and a controlled release layer. The examiner asserted that it would have been obvious to use the drug combination taught by Suhner in the dual layer tablet taught by Richardson. This rejection is traversed.

The deficiencies of the Suhner and Ohkawa references have been discussed above, and that discussion is equally applicable to the present rejection. The teachings of the tertiary Richardson reference do not compensate for the shortcomings of the primary and secondary references. The cited references, whether alone or in combination, do not suggest the administration of melatonin and a non-benzodiazepine hypnotic to promote sleep initiation for a person who has difficulty falling asleep, wherein the melatonin is administered in an amount

effective to potentiate the non-benzodiazepine compound's hypnotic effect.

Claims 29-31 and 34-37 have been rejected under 35 U.S.C. § 103(a) as unpatentable over the Ohkawa reference. The examiner asserted that the reference teaches administering a melatonin agonist in combination with another drug, such a zolpidem to treat sleep disorders, including primary insomnia. This rejection is traversed.

As Applicants have noted above, one of skill in the art reading the complete Ohkawa reference, including the Experimental Example bridging columns 9 and 10 would come away believing that the combination of one particular melatonin agonist and one of four specific selected benzodiazepine and non-benzodiazepine compounds taught by Ohkawa would have an impact on sleep disorders only by affecting the latencies of stage 3 and stage 4 sleep. This is very different from Applicants' discovery that the administration of melatonin and a non-benzodiazepine hypnotic drug can promote sleep initiation in a human who has difficulty falling asleep. Based on the teachings of the Ohkawa's example, one of skill in the art would interpret Ohkawa's reference to treating sleep disorders as meaning that sleep quality could be affected, not that sleep initiation could be affected.

Claims 32 and 33 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Ohkawa in view of Richardson. The Ohkawa reference was applied as in the previous rejection, and Richardson was cited as in the rejection above of claims 32 and 33. This rejection is traversed.

The deficiencies of the Ohkawa reference have been discussed at length above, and that discussion is equally applicable to the present rejection. The teachings of the Richardson patent do not

compensate for the shortcomings of Ohkawa. There is nothing in either reference, taken together or independently that suggests that melatonin and a non-benzodiazepine hypnotic can be administered to promote sleep initiation.

Applicants respectfully submit that the pending claims as amended are patentable over the cited references.

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